Published in final edited form as:
Am J Med Genet B Neuropsychiatr Genet. 2008 July 5; 147B(5): 661–666. doi:10.1002/ajmg.b.30656.

Association Study Between the Serotonin 1A Receptor (HTR1A) Gene and Neuroticism, Major Depression, and Anxiety Disorders

J.M. Hettema[1,*], **S.S. An**[1], **E.J.C.G van den Oord**[1,3], **M.C. Neale**[1,2], **K.S. Kendler**[1,2], and **X. Chen**[1]

[1]Department of Psychiatry, Virginia Institute for Psychiatric and Behavioral Genetics, Virginia Commonwealth University, Richmond, Virginia

[2]Department of Human Genetics, Virginia Institute for Psychiatric and Behavioral Genetics, Virginia Commonwealth University, Richmond, Virginia

[3]Department of Pharmacy, Center for Biomarker Research and Personalized Medicine, Virginia Commonwealth University, Richmond, Virginia

Abstract

The serotonin neurotransmitter system in general, and the serotonin 1A receptor in particular, has been broadly implicated in the pathophysiology of mood and anxiety disorders, although the results of genetic association studies have been mixed. In this study, we examined the serotonin 1A receptor gene, *HTR1A*, for its association with shared genetic risk across a range of anxiety and depression-related phenotypes. Using multivariate structural equation modeling, we selected twin pairs from the population-based Virginia Adult Twin Study of Psychiatric and Substance Use Disorders scoring at the extremes of a latent genetic risk factor that underlies susceptibility to neuroticism, major depression, and several anxiety disorders. One member from each selected pair was entered into a 2-stage, case-control association study for the *HTR1A* gene. In the resulting sample of 589 cases and 539 controls, four SNPs spanning the *HTR1A* locus, including the C(−1019)G functional promoter polymorphism (rs6295), were screened in stage 1, the positive results of which were tested for replication in stage 2. While one marker met threshold significance criteria in stage 1, this association was not replicated in stage 2. Post-hoc analyses did not reveal association to any of the specific psychiatric phenotypes. Our data suggests that the *HTR1A* gene may not play a major role in the genetic susceptibility underlying depressive and anxiety-related phenotypes.

Keywords

serotonin; depression; anxiety; personality; association study; genetics

INTRODUCTION

Among the various components of the serotonin transmitter system, the serotonin 1A (5-HT1A) receptor has been strongly implicated in the pathophysiology of anxiety and depressive states across phylogeny. Several groups have shown that 5-HT1A receptor knock-out mice exhibit a range of increased fear-related behaviors (see Gross et al. [2000]

*Correspondence to: Dr. J.M. Hettema, Department of Psychiatry, Virginia Institute for Psychiatric and Behavioral Genetics, P.O. Box 980126, Richmond, Virginia 23298-0126. jhettema@vcu.edu.

and Toth [2003] for reviews). Complimentary to this, mutant mice that over-expressed 5-HT1A receptor during development show reduced anxiety-related behaviors [Kusserow et al., 2004]. In amygdala-kindled rats, fear levels were significantly correlated with 5-HT1A receptor binding and mRNA expression in the hippocampus [Kalynchuk et al., 2006]. Multiple brain regions in monkeys exhibiting symptoms of behavioral depression showed reduced 5-HT1A receptor binding via PET imaging [Shively et al., 2006]. Similarly, studies have demonstrated altered 5-HT1A receptor binding in human subjects with elevated neuroticism levels [Tauscher et al., 2001], major depression [Meltzer et al., 2004; Parsey et al., 2006], anxious depression [Sullivan et al., 2005], panic disorder [Neumeister et al., 2004], and social phobia [Lanzenberger et al., 2007], although not in subjects with posttraumatic stress disorder [Bonne et al., 2005]. 5-HT1A receptor agonists decrease anxiety-related behaviors and show utility for treating anxiety [Feighner and Boyer, 1989] and possibly depressive disorders [Blier and Ward, 2003].

The gene coding the 5-HT1A receptor, *HTR1A*, is small (1.27 Kb) and intronless, located on the long arm of chromosome 5. Several early studies failed to find association of several rare functional variants of this gene with various psychiatric phenotypes [Erdmann et al., 1995; Kawanishi et al., 1998; Nishiguchi et al., 2002]. A common single nucleotide polymorphism (SNP rs6295) in the promoter region, C(−1019)G [Wu and Comings, 1999] has been shown to regulate transcription by binding the transcription factor NUD8 [Albert and Lemonde, 2004], but evidence relating this polymorphism to psychiatric phenotypes has been mixed, as indicated in Table I. While Strobel et al. [2003] reported significant association of the G allele with anxiety-related traits of neuroticism and harm avoidance in healthy volunteers, this was not replicated in a sample of alcohol dependent subjects [Koller et al., 2006]. Lemonde et al. [2003] reported highly significant association of the G allele in separate Canadian cohorts compared for major depression (129 cases, 134 controls; $P = 0.0006$) and suicide completion (102 completers, 116 normal controls; $P = 0.00008$). However, two larger follow-up case control studies failed to detect significant association of this polymorphism with major depression [Arias et al., 2002; Huang et al., 2004]. Besides major depression, the latter study by Huang et al. examined multiple psychiatric phenotypes including panic disorder in relation to C(−1019)G, but only found association with schizophrenia, substance use disorders, and panic attacks. A prior study of German patients with panic disorder found a trend for association of the G allele with panic disorder that became marginally significant ($P = 0.03$) when restricted to those cases identified as having panic disorder with agoraphobia (n = 101) [Rothe et al., 2004]. The connection between the various 5-HT1A receptor binding alterations cited earlier and these genetic association findings is unclear, as genotype at the C(−1019)G polymorphism was unrelated to receptor binding in a PET study in 140 healthy volunteers [David et al., 2005].

Given the current uncertainty of the role, if any, of *HTR1A* in human psychopathology, and the diversity of internalizing phenotypes for which associations with *HTR1A* have been reported, in this study we sought to assess the potential association between *HTR1A* gene variants and shared genetic risk across a range of depressive and anxiety-related phenotypes in a large, population-based sample. Specifically, we tested the C(−1019)G promoter polymorphism as well as other markers that characterize the major allelic variation around the *HTR1A* locus.

MATERIALS AND METHODS

Subjects

The subjects in this study derive from the population-based Virginia Adult Twin Study of Psychiatric and Substance Use Disorders (VATSPSUD) [Kendler and Prescott, 1999; Kendler and Prescott, 2006]. All subjects were Caucasian and born in Virginia. Approval of

the local Institutional Review Board was obtained prior to the study and informed consent was obtained from all subjects prior to data collection.

Diagnostic Measures

We obtained lifetime psychiatric diagnoses via face-to-face or telephone structured psychiatric interview based on the SCID [Spitzer and Williams, 1985]. We used DSM-III-R [American Psychiatric Association, 1987] diagnostic criteria to assess lifetime major depression, and modified DSM-III-R criteria for lifetime generalized anxiety disorder and panic disorder [Hettema et al., 2001; Kendler et al., 2001a]. Phobia was diagnosed using an adaptation of DSM-III criteria [American Psychiatric Association, 1980] which required the presence of one or more of 22 fears which the respondent recognized as unreasonable and that, in the judgment of the interviewer, objectively interfered with the respondent's life [Kendler et al., 2001b]. We included agoraphobia and social phobia in the phenotypic modeling used for this study (see below). Neuroticism was assessed using the 12 items from the short form of the Eysenck Personality Questionnaire (EPQ) [Eysenck and Eysenck, 1975] via self-report questionnaire. It was analyzed as an ordinal variable with scores from 0 to 12.

Sample Selection

As described previously [Hettema et al., 2006a], we used a two-stage association design in which candidate loci were screened in stage 1, the positive results of which were tested for replication in stage 2. The parameters for this design were calculated using the LGA program [Robles and van den Oord, 2004] to achieve 80% power to detect markers that explained 1% of the variance of the liability distribution while controlling the false discovery rate at 0.1 [van den Oord and Sullivan, 2003]. Using the extreme selection strategy outlined below, LGA indicated that we needed about 350 subjects in the stage 1 and 1,000 in the stage 2 sample. If any of the markers genotyped in stage 1 met the estimated threshold *P*-value of 0.1 or less, they were then also tested in the stage 2 sample.

We have incorporated two novel strategies into our subject selection procedure. First, we have taken advantage of the extant literature that suggests shared genetic susceptibility among neuroticism, the anxiety disorders, and major depression [Jardine et al., 1984; Scherrer et al., 2000; Middeldorp et al., 2005; Hettema et al., 2006b]. Starting with a total of 9270 twin subjects, we used multivariate structural equation modeling to estimate a latent genetic risk factor for neuroticism that is highly correlated (range 0.6–0.8) with genetic susceptibility to major depression, generalized anxiety disorder, panic disorder, agoraphobia, and social phobia (see Hettema et al. [2006b] for details). Like phenotypic factor analysis, the factor derived from this analysis combines information across the correlated measures (phenotypes), but in this case uses shared genetic risk as the basis for this combination. Second, several authors have proposed using extreme phenotypic selection schemes to maximize the difference in information contained in a sample of subjects assessed on continuous measures such as blood pressure or depression scores [van den Oord, 1999; Schork et al., 2000; Van Gestel et al., 2000]. However, unlike these selection schemes based only upon *phenotypic* extremes, the use of a genetically informative sample containing twins allows for the identification of subjects who are at the high and low extremes of *genetic risk* as well, as estimated by the twin pair's score on the above-mentioned genetic factor. Selecting subjects from the extremes of their underling genetic risk factor should provide a powerful method for detecting genes of small effect expected to contribute to complex genetic phenotypes like psychiatric disorders. One member from each twin pair for whom DNA was available was selected as a case or control based upon scoring above the 80th or below the 20th percentile, respectively, of the genetic factor extracted from the above analysis. This produced a total sample size N = 1,128 consisting of 589 cases and 539

controls, of which 376 and 752 were used in stage 1 and stage 2 respectively. We note that this is more than just a selection on neuroticism, as, for example, some pairs score in the upper tail due to high genetic loading on MDD, GAD, etc. and may have relatively low levels of neuroticism. Overall, the cases had a mean raw neuroticism score of 6.3 (z-score = 1.04) and had the following frequencies of the target psychiatric illnesses: major depressive disorder (80.1%), generalized anxiety disorder (53.8%), panic disorder (20.5%), agoraphobia (14.1%), and social phobia (17.5%). The controls were free of these five disorders and had a mean raw neuroticism score of 0.55 (z-score = −0.89). The phenotypic distributions did not differ significantly between the stage 1 and stage 2 samples. However, while stage 1 subjects were selected so that the sexes were equally distributed to maximize power to detect any sex-specific associations, the stage 2 male-female make-up was about 2:1.

Genotyping

Subjects were instructed to use standard cytology brushes to obtain buccal epithelial cells for DNA extraction. The method for DNA extraction from the cytology brushes was described previously [Straub et al., 1999]. SNPs were genotyped by the 5′ nuclease cleavage assay (also called TaqMan method) [Livak, 1999]. Reactions were performed in 384-well plates with 5 μl reaction volume containing 0.25 μl of 20× Assays-on-Demand™ SNP assay mix, 2.5 μl of TaqMan universal PCR master mix, and 5 ng of genomic DNA. The conditions for PCR were initial denaturizing at 95°C for 10 min, followed by 40 cycles of 92°C for 15 sec and 60°C for 1 min. After the reaction, fluorescence intensities for reporter 1 (VIC, excitation = 520 ± 10 nm, emission = 550 ± 10 nm) and reporter 2 (FAM, excitation = 490 ± 10 nm, emission = 510 ± 10 nm) were read by the Analyst fluorescence plate reader (LJL Biosytems, Sunnyvale, CA). Genotypes were scored by a Euclidian clustering algorithm developed in our laboratory. All genotyped SNPs were checked for deviations from Hardy–Weinberg equilibrium.

HTR1A is an intronless gene that spans a 1.27 Kb interval on 5q12.3. While several exonic SNP polymorphisms are listed in dbSNP, none are known to have significant minor allele frequencies in Caucasian samples. Therefore, in addition to the C(−1019)G promoter polymorphism rs6295, we selected other SNP markers in an approximately 16 Kb interval that is part of a larger haplotype block around the *HTR1A* gene with the aim to tag the major haplotypes (frequency>1–2%) in that interval observed in the Caucasian panel used by the TIHMP [2003]. We used the Tagger module of HAPLOVIEW 3.2 [Barrett et al., 2005] with HapMap Phase II data, specifying aggressive tagging of 2- and 3-marker haplotypes and a threshold of $r^2 = 0.8$. In all, we genotyped four SNPs around the *HTR1A* locus.

Statistical Analysis

Pearson's chi-squared tests were used to test for allelic or genotypic differences by marker between cases and controls in the two stages. We then used HAPLOVIEW 3.2 [Barrett et al., 2005] to find the regions of high LD (i.e., haplotype blocks) using the default confidence interval algorithm [Gabriel et al., 2002]. Haplotype association analyses were performed for markers within the same haplotype block with the Cocaphase module of the UNPHASED program [Dudbridge, 2003]. UNPHASED uses the expectation-maximization algorithm [Excoffier and Slatkin, 1995] to estimate the haplotypes and their frequencies.

RESULTS

The genotype and allele frequencies and results of chi-squared association tests for the four *HTR1A* markers genotyped in stages 1 and 2 are listed in Table II and Table III, respectively. None of the SNPs showed deviations from Hardy–Weinberg equilibrium. Only

marker 1 (rs1364043) met threshold criteria of allelic *P*-value <0.1 in our stage 1 sample; however, this association was not replicated in stage 2. We attempted to genotype one (synonymous) coding SNP within the gene (rs6294), but it was monomorphic, consistent with data in dbSNP.

To better understand the LD structure, we constructed haplotype blocks using the default block search procedure [Gabriel et al., 2002] in HAPLOVIEW 3.2. Markers 1, 2, and 3 occurred on a single haplotype block in our sample, although LD between these markers and marker 4 was high (D′ >0.9), consistent with CEU HapMap data. We therefore analyzed association of sliding-window haplotypes created from combinations of all of our SNP markers. In Table IV, we present the results, by stage, for the 4-marker haplotypes formed from these SNPs as calculated using the Cocaphase module of UNPHASED. (Results for shorter 2- and 3-marker haplotypes produced similar patterns.) As indicated, while several of the marker combinations showed near-significant haplotypic differences between cases and controls, these came from low frequency haplotypes that were not consistent across stages. Post-hoc analyses by sex did not provide any additional evidence of association from individual markers or haplotypes.

Given prior reported associations between the C(−1019)G promoter polymorphism rs6295 and several of our phenotypes, we tested this marker for association with all of the relevant specific phenotypes within our total sample. Using Cochran–Mantel–Haenszel tests in the FREQ procedure and regression analysis in the GENMOD procedure in SAS Institute [1999], we were unable to detect associations with major depression (N_{cases} = 463), generalized anxiety disorder (N_{cases} = 317), panic disorder (N_{cases} = 122), agoraphobia (N_{cases} = 83), social phobia (N_{cases} = 104), or neuroticism (N = 1063).

DISCUSSION

In this study, we sought to test whether the *HTR1A* gene is associated with susceptibility to human internalizing phenotypes, including major depression, a range of anxiety disorders, and neuroticism. This susceptibility was indexed by a latent genetic factor common to these phenotypes, the score of which we derived from multivariate twin modeling and subsequently used to select subjects at the extremes of genetic risk. We entered the resulting sample of 589 cases and 539 controls into a two-stage association study in which markers from the candidate locus were screened in stage 1, the positive results of which were tested for replication in stage 2. While prior studies had focused on the promoter region C(−1019)G polymorphism (rs6295), we genotyped this plus three other SNPs that accounted for the major allelic variation across this gene.

Out of the four markers tested in the *HTR1A* gene, only one met the threshold criterion in stage 1 of $P < 0.1$ to be considered for genotyping in the stage 2 sample, but this association was not replicated in stage 2. Multi-marker haplotypes also failed to show consistent association across the two stages. Furthermore, given prior reported associations between the C(−1019)G promoter polymorphism and major depression, panic disorder, and neuroticism, we tested this marker for association with each specific phenotype within our total sample, failing to detect any significant association. This is consistent with some, but not all, of prior studies. Given that this is the largest sample used to test association with these phenotypes, our data suggests there is little evidence for association of the *HTR1A* gene with these depressive and anxiety-related phenotypes.

The results of this study should be interpreted in the context of several potential limitations. First, we investigated the potential association between the *HTR1A* gene in subjects selected for scoring at the extremes of a latent genetic risk factor shared among a group of depressive

and anxiety spectrum phenotypes. While this unique selection strategy may maximize power to detect a subset of susceptibility genes common across several psychiatric disorders, it is different from the typical clinically-assessed cases used in several of the prior studies. Although all of our high risk subjects had one or more of the target psychiatric phenotypes, it is unclear how such potential differences may affect comparability between this and prior studies. Second, although this is the largest sample used thus far to test for association of the *HTR1A* gene with these psychiatric conditions, it may nonetheless lack sufficient power to detect association (if it exists) for some of the less prevalent phenotypes. Third, while we chose SNP markers designed to capture the major allelic variation across the *HTR1A* locus and tagged all of the common haplotypes, we did not test for effects from exonic coding SNPs within the gene. Furthermore, even a sample as large as ours is likely underpowered to detect the effects of rare SNPs or haplotypes. Finally, we did not test the effects of gene-by-environment interactions.

In summary, this study does not support an association between the *HTR1A* gene and individual differences in neuroticism or susceptibility to depressive or anxiety disorders. This does not contradict other studies that find a strong link between functionality of the HTR1A receptor and related phenotypes; our findings only suggest that *HTR1A* genetic variation alone is unlikely to cause these effects.

Acknowledgments

This work was supported by NIH grants MH-40828, MH-65322, MH-20030, DA-11287, MH/AA/DA-49492 (KSK), and K08 MH-66277-1, a NARSAD Young Investigator Award, and a Pfizer/SWHR Scholars Award (JMH). We acknowledge the contribution of the Virginia Twin Registry, now part of the Mid-Atlantic Twin Registry (MATR), to ascertainment of subjects for this study. The MATR, directed by Dr. J. Silberg and Dr. L. Eaves, has received support from the National Institutes of Health, the Carman Trust and the WM Keck, John Templeton and Robert Wood Johnson Foundations.

Grant sponsor: NIH; Grant numbers: MH-40828, MH-65322, MH-20030, DA-11287, MH/AA/DA-49492, K08 MH-66277-1.

REFERENCES

Albert PR, Lemonde S. 5-HT1A receptors, gene repression, and depression: Guilt by association. Neuroscientist 2004;10:575–593. [PubMed: 15534042]

American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 3rd editionWashington, DC: American Psychiatric Association; 1980.

American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 3rd editionWashington, DC: American Psychiatric Association; 1987. Revised

Arias B, Arranz MJ, Gasto C, Catalan R, Pintor L, Gutierrez B, Kerwin RW, Fananas L. Analysis of structural polymorphisms and C-1018G promoter variant of the 5-HT(1A) receptor gene as putative risk factors in major depression. Mol Psychiatry 2002;7:930–932. [PubMed: 12399944]

Barrett JC, Fry B, Maller J, Daly MJ. Haploview: Analysis and visualization of LD and haplotype maps. Bioinformatics 2005;21:263–265. [PubMed: 15297300]

Blier P, Ward NM. Is there a role for 5-HT1A agonists in the treatment of depression? Biol Psychiatry 2003;53:193–203. [PubMed: 12559651]

Bonne O, Bain E, Neumeister A, Nugent AC, Vythilingam M, Carson RE, Luckenbaugh DA, Eckelman W, Herscovitch P, Drevets WC, Charney DS. No change in serotonin type 1A receptor binding in patients with posttraumatic stress disorder. Am J Psychiatry 2005;162:383–385. [PubMed: 15677606]

David SP, Murthy NV, Rabiner EA, Munafo MR, Johnstone EC, Jacob R, Walton RT, Grasby PM. A functional genetic variation of the serotonin (5-HT) transporter affects 5-HT1A receptor binding in humans. J Neurosci 2005;25:2586–2590. [PubMed: 15758168]

Dudbridge F. Pedigree disequilibriumtests for multilocus haplotypes. Genet Epidemiol 2003;25:115–121. [PubMed: 12916020]

Erdmann J, Shimron-Abarbanell D, Cichon S, Albus M, Maier W, Lichtermann D, Minges J, Reuner U, Franzek E, Ertl MA, et al. Systematic screening for mutations in the promoter and the coding region of the 5-HT1A gene. Am J Med Genet 1995;60:393–399. [PubMed: 8546152]

Excoffier L, Slatkin M. Maximum-likelihood estimation of molecular haplotype frequencies in a diploid population. Mol Biol Evol 1995;12:921–927. [PubMed: 7476138]

Eysenck, HJ.; Eysenck, SBG. Manual of the eysenck personality questionnaire. London: Hodder and Stoughton; 1975.

Feighner JP, Boyer WF. Serotonin-1A anxiolytics: An overview. Psychopathology 1989;22:21–26. [PubMed: 2567039]

Gabriel SB, Schaffner SF, Nguyen H, Moore JM, Roy J, Blumenstiel B, Higgins J, DeFelice M, Lochner A, Faggart M, Liu-Cordero SN, Rotimi C, Adeyemo A, Cooper R, Ward R, Lander ES, Daly MJ, Altshuler D. The structure of haplotype blocks in the human genome. Science 2002;296:2225–2229. [PubMed: 12029063]

Gross C, Santarelli L, Brunner D, Zhuang X, Hen R. Altered fear circuits in 5-HT(1A) receptor KO mice. Biol Psychiatry 2000;48:1157–1163. [PubMed: 11137057]

Hettema JM, Prescott CA, Kendler KS. A population-based twin study of generalized anxiety disorder in men and women. J Nerv Ment Dis 2001;189:413–420. [PubMed: 11504317]

Hettema JM, An SS, Neale MC, Bukszar J, van den Oord EJ, Kendler KS, Chen X. Association between glutamic acid decarboxylase genes and anxiety disorders, major depression, and neuroticism. Mol Psychiatry 2006a;11:752–762. [PubMed: 16718280]

Hettema JM, Neale MC, Myers JM, Prescott CA, Kendler KS. A population-based twin study of the relationship between neuroticism and internalizing disorders. Am J Psychiatry 2006b;163:857–864. [PubMed: 16648327]

Huang YY, Battistuzzi C, Oquendo MA, Harkavy-Friedman J, Greenhill L, Zalsman G, Brodsky B, Arango V, Brent DA, Mann JJ. Human 5-HT1A receptor C(−1019)G polymorphism and psychopathology. Int J Neuropsychopharmacol 2004;7:441–451. [PubMed: 15469667]

Jardine R, Martin NG, Henderson AS. Genetic covariation between neuroticism and the symptoms of anxiety and depression. Genet Epidemiol 1984;1:89–107. [PubMed: 6544237]

Kalynchuk LE, Pinel JP, Meaney MJ. Serotonin receptor binding and mRNA expression in the hippocampus of fearful amygdala-kindled rats. Neurosci Lett 2006;396:38–43. [PubMed: 16324784]

Kawanishi Y, Harada S, Tachikawa H, Okubo T, Shiraishi H. Novel mutations in the promoter and coding region of the human 5-HT1A receptor gene and association analysis in schizophrenia. Am J Med Genet 1998;81:434–439. [PubMed: 9754630]

Kendler KS, Prescott CA. A population-based twin study of lifetime major depression in men and women. Arch Gen Psychiatry 1999;56:39–44. [PubMed: 9892254]

Kendler, KS.; Prescott, CA. Genes, environment, and psychopathology: Understanding the causes of psychiatric and substance use disorders. New York: Guilford Press; 2006.

Kendler KS, Gardner CO, Prescott CA. Panic syndromes in a population-based sample of male and female twins. Psychol Med 2001a;31:989–1000. [PubMed: 11513384]

Kendler KS, Myers J, Prescott CA, Neale MC. The genetic epidemiology of irrational fears and phobias in men. Arch Gen Psychiatry 2001b;58:257–265. [PubMed: 11231833]

Koller G, Bondy B, Preuss UW, Zill P, Soyka M. The C(−1019)G 5-HT1A promoter polymorphism and personality traits: No evidence for significant association in alcoholic patients. Behav Brain Funct 2006;2:7. [PubMed: 16504134]

Kusserow H, Davies B, Hortnagl H, Voigt I, Stroh T, Bert B, Deng DR, Fink H, Veh RW, Theuring F. Reduced anxiety-related behaviour in transgenic mice overexpressing serotonin 1A receptors. Brain Res Mol Brain Res 2004;129:104–116. [PubMed: 15469887]

Lanzenberger RR, Mitterhauser M, Spindelegger C, Wadsak W, Klein N, Mien LK, Holik A, Attarbaschi T, Mossaheb N, Sacher J, Geiss-Granadia T, Kletter K, Kasper S, Tauscher J. Reduced serotonin-1Areceptor binding in social anxiety disorder. Biol Psychiatry 2007;61:1081–1089. [PubMed: 16979141]

Lemonde S, Turecki G, Bakish D, Du L, Hrdina PD, Bown CD, Sequeira A, Kushwaha N, Morris SJ, Basak A, Ou XM, Albert PR. Impaired repression at a 5-hydroxytryptamine 1A receptor gene polymorphism associated with major depression and suicide. J Neurosci 2003;23:8788–8799. [PubMed: 14507979]

Livak KJ. Allelic discrimination using fluorogenic probes and the 5′ nuclease assay. Genet Anal 1999;14:143–149. [PubMed: 10084106]

Meltzer CC, Price JC, Mathis CA, Butters MA, Ziolko SK, Moses-Kolko E, Mazumdar S, Mulsant BH, Houck PR, Lopresti BJ, Weissfeld LA, Reynolds CF. Serotonin 1A receptor binding and treatment response in late-life depression. Neuropsychopharmacology 2004;29:2258–2265. [PubMed: 15483563]

Middeldorp CM, Cath DC, VanDyck R, Boomsma DI. The co-morbidity of anxiety and depression in the perspective of genetic epidemiology. A review of twin and family studies. Psychol Med 2005;35:611–624. [PubMed: 15918338]

Neumeister A, Bain E, Nugent AC, Carson RE, Bonne O, Luckenbaugh DA, Eckelman W, Herscovitch P, Charney DS, Drevets WC. Reduced serotonin type 1A receptor binding in panic disorder. J Neurosci 2004;24:589–591. [PubMed: 14736842]

Nishiguchi N, Shirakawa O, Ono H, Nishimura A, Nushida H, Ueno Y, Maeda K. Lack of an association between 5-HT1A receptor gene structural polymorphisms and suicide victims. Am J Med Genet 2002;114:423–425. [PubMed: 11992564]

Parsey RV, Oquendo MA, Ogden RT, Olvet DM, Simpson N, Huang YY, Van Heertum RL, Arango V, Mann JJ. Altered serotonin 1A binding in major depression: A [carbonyl-C-11]WAY100635 positron emission tomography study. Biol Psychiatry 2006;59:106–113. [PubMed: 16154547]

Robles JR, van den Oord EJ. lga972: A cross-platform application for optimizing LD studies using a genetic algorithm. Bioinformatics 2004;20:3244–3245. [PubMed: 15180931]

Rothe C, Gutknecht L, Freitag C, Tauber R, Mossner R, Franke P, Fritze J, Wagner G, Peikert G, Wenda B, Sand P, Jacob C, Rietschel M, Nothen MM, Garritsen H, Fimmers R, Deckert J, Lesch KP. Association of a functional 1019C> G 5-HT1A receptor gene polymorphism with HTR1A and Depression/Anxiety 665 panic disorder with agoraphobia. Int J Neuropsychopharmacol 2004;7:189–192. [PubMed: 14984628]

SAS Institute. SAS/STAT Software: Version 8. Cary, NC: SAS Institute Inc.; 1999.

Scherrer JF, True WR, Xian H, Lyons MJ, Eisen SA, Goldberg J, Lin N, Tsuang MT. Evidence for genetic influences common and specific to symptoms of generalized anxiety and panic. J Affect Disord 2000;57:25–35. [PubMed: 10708813]

Schork NJ, Nath SK, Fallin D, Chakravarti A. Linkage disequilibrium analysis of biallelic DNA markers, human quantitative trait loci, and threshold-defined case and control subjects. Am J Hum Genet 2000;67:1208–1218. [PubMed: 11032785]

Shively CA, Friedman DP, Gage HD, Bounds MC, Brown-Proctor C, Blair JB, Henderson JA, Smith MA, Buchheimer N. Behavioral depression and positron emission tomography-determined serotonin 1A receptor binding potential in cynomolgus monkeys. Arch Gen Psychiatry 2006;63:396–403. [PubMed: 16585468]

Spitzer, RL.; Williams, JBW. Biometrics Research Department. New York: New York State Psychiatric Institute; 1985. Structured clinical interview for DSM-III-R (SCID).

Straub RE, Sullivan PF, Ma Y, Myakishev MV, Harris-Kerr C, Wormley B, Kadambi B, Sadek H, Silverman MA, Webb BT, Neale MC, Bulik CM, Joyce PR, Kendler KS. Susceptibility genes for nicotine dependence: A genome scan and followup in an independent sample suggest that regions on chromosomes 2, 4, 10, 16,17 and 18 merit further study. Mol Psychiatry 1999;4:129–144. [PubMed: 10208445]

Strobel A, Gutknecht L, Rothe C, Reif A, Mossner R, Zeng Y, Brocke B, Lesch KP. Allelic variation in 5-HT1A receptor expression is associated with anxiety- and depression-related personality traits. J Neural Transm 2003;110:1445–1453. [PubMed: 14666415]

Sullivan GM, Oquendo MA, Simpson N, Van Heertum RL, John MJ, Parsey RV. Brain Serotonin(1A) Receptor Binding in Major Depression Is Related to Psychic and Somatic Anxiety. Biol Psychiatry 2005;58(12):947–954. [PubMed: 16039621]

Tauscher J, Bagby RM, Javanmard M, Christensen BK, Kasper S, Kapur S. Inverse relationship between serotonin 5-HT(1A) receptor binding and anxiety: A [(11)C]WAY-100635 PET investigation in healthy volunteers. Am J Psychiatry 2001;158:1326–1328. [PubMed: 11481173]

The International HapMap Project. Nature 2003;426:789–796. [PubMed: 14685227]

Toth M. 5-HT1A receptor knockout mouse as a genetic model of anxiety. Eur J Pharmacol 2003;463:177–184. [PubMed: 12600709]

van den Oord EJCG. A comparison between different designs and tests to detect QTLs in association studies. Behav Genet 1999;29:245–256.

van den Oord EJ, Sullivan PF. False discoveries and models for gene discovery. Trends Genet 2003;19:537–542. [PubMed: 14550627]

Van Gestel S, Houwing-Duistermaat JJ, Adolfsson R, van Duijn CM, Van Broeckhoven C. Power of selective genotyping in genetic association analyses of quantitative traits. Behav Genet 2000;30:141–146. [PubMed: 10979604]

Wu S, Comings DE. A common C-1018G polymorphism in the human 5-HT1A receptor gene. Psychiatr Genet 1999;9:105–106. [PubMed: 10412191]

TABLE I

Genetic Association Studies of *HTR1A* C(−1019)G Polymorphism in Depression- and Anxiety-Related Phenotypes

Study	Phenotype	N (cases, controls)	Association (allele)	Comments
Strobel et al. [2003]	NEO and TPQ	284	+ (G)	Associations with N (P = 0.025) and HA (P = 0.033)
Koller et al. [2006]	NEO and TCI	185	−	Alcohol-dependent subjects
Lemonde et al. [2003]	MDD	129, 134	+ (G)	P = 0.0006
Arias et al. [2002]	MDD	249, 170	−	
Huang et al. [2004]	MDD	328, 107	−	
	PD	87, 107	−	G allele associated with PA (P = 0.013)
Rothe et al. [2004]	PD	134, 134	+ (G)	+ only in subgroup with AG (P = 0.03)

NEO, NEO personality inventory; TPQ, tridimensional personality questionnaire; TCI, temperament and character inventory; N, neuroticism; HA, harm avoidance; MDD, major depressive disorder; SCZ, schizophrenia; SUD, substance use disorder; PD, panic disorder; PA, panic attack; AG, agoraphobia.

TABLE II

HTR1A Individual Marker Association Results for Stage 1 (N = 188 Cases, 188 Controls)

Marker	Marker ID (dbSNP)	Alleles (major)	Group	Genotypes (%)			Genotypic *P*-value	Alleles (%)		Allelic *P*-value
				A1/A1	A1/A2	A2/A2		A1	A2	
1	rs1364043	G/T	Cases	59.0	34.6	6.4	0.085	76.3	23.7	0.059
		(T)	Controls	66.0	31.9	2.1		81.9	18.1	
2	rs1423691	C/T	Cases	27.2	47.1	25.7	0.899	50.8	49.2	0.714
		(T)	Controls	29.4	45.5	25.1		52.1	47.9	
3	rs878567	C/T	Cases	28.0	46.2	25.8	0.961	51.9	48.9	0.830
		(T)	Controls	29.3	45.2	25.5		51.1	48.1	
4	rs6295	C/G	Cases	27.8	47.1	25.1	0.930	51.3	48.7	0.886
		(G)	Controls	29.3	45.2	25.5		51.9	48.1	

Am J Med Genet B Neuropsychiatr Genet. Author manuscript; available in PMC 2010 April 25.

TABLE III

HTR1A Individual Marker Association Results for Stage 2 (N = 401 Cases, 351 Controls)

Marker	Marker ID (dbSNP)	Alleles (major)	Group	Genotypes (%)			Genotypic *P*-value	Alleles (%)		Allelic *P*-value
				A1/A1	A1/A2	A2/A2		A1	A2	
1	rs1364043	G/T	Cases	59.0	33.8	7.3	0.888	75.9	24.1	0.630
		(T)	Controls	60.7	32.4	6.9		76.9	23.1	
2	rs1423691	C/T	Cases	30.5	45.7	23.8	0.876	53.4	46.6	0.962
		(T)	Controls	29.4	47.7	22.9		53.2	46.8	
3	rs878567	C/T	Cases	30.8	46.4	22.8	0.469	54.0	46.0	0.411
		(T)	Controls	26.9	50.0	23.1		51.9	48.1	
4	rs6295	C/G	Cases	30.4	47.1	22.5	0.591	54.0	46.0	0.389
		(G)	Controls	27	49.4	23.6		51.7	48.3	

TABLE IV

HTR1A Haplotype Analysis Results for Stage 1 and Stage 2

Stage	Markers	Global *P*-value	Haplotype	Frequency cases	Frequency controls	Haplotype *P*-value
1	1, 2, 3, 4	0.035	1-1-1-1	0.480	0.513	0.377
			1-1-1-2	0.022	<0.01	0.116
			1-2-2-1	0.100	<0.01	0.080
			1-2-2-2	0.242	0.294	0.108
			2-2-2-1	0.011	<0.01	0.158
			2-2-2-2	0.228	0.179	0.096
2	1, 2, 3, 4	0.091	1-1-1-1	0.445	0.458	0.646
			1-1-1-2	0.015	<0.01	0.048
			1-2-2-1	<0.01	<0.01	0.849
			1-2-2-2	0.290	0.283	0.760
			2-2-2-1	<0.01	<0.01	0.045
			2-2-2-2	0.228	0.226	0.921

“1” represents the major allele and “2” the minor allele, respectively, for each SNP marker in a haplotype.